N9810.0029/P029

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Harry A. Dugger, III et al.

Application No.: 10/671,720 Confirmation No.: 9272

Filed: September 29, 2003 Art Unit: 1616

For: BUCCAL, POLAR AND NON-POLAR SPRAY CONTAINING ALPRAZOLAM Examiner: M. Haghighatian

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF FRANK E. BLONDINO, PhD. UNDER 37 CFR 1.132

Dear Sir:

I, Dr. Frank E. Blondino, declare and state as follows:

1. I am of legal age, and under no disability that prevents me from attesting to the following statements and information, which are based on my personal knowledge and observations or on my best information and belief.

2. I reside at 118 Knollwood Drive, Easton, PA 18042.

3. I am Executive Director of Formulation and Process Development for NovaDel Pharma Inc., the assignee of U.S. Patent Application 10/671,720 (the "'720 application"). My responsibilities as Executive Director of Formulation and Process Development include overseeing and developing formulations for various pharmaceutical compositions, including buccal spray compositions.

4. I have read and understand the claims and specification of the '720 application.

5. Further, I am familiar with pharmacokinetic/pharmacodynamic studies designed to evaluate overall comparability of the pharmacokinetic profile of an alprazolam oral spray and alprazolam tablets as determined by Cmax and AUCs. The studies' objectives also included comparative evaluation of metrics of the speed of drug absorption and pharmacodynamic properties of the alprazolam oral spray as well as evaluation of its safety and tolerability profile.

6. Data from the studies is provided in Exhibit A hereto. As shown by the data, the alprazolam oral spray was surprisingly effective and superior to administration by oral tablet. The results demonstrate a significantly faster rate of drug absorption for the oral spray formulations. Oral spray groups consistently outperformed oral tablet with statistically significant differences reported for a number of pharmacodynamic parameters.

7. The highest oral spray dose (1 mg dose administered over the tongue) demonstrated faster absorption when compared to the oral tablet. After dose-adjustment, concentration level and total amount of drug delivered by 15 minutes post-dosing were approximately 40 % higher than in the oral tablet group.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. All statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified patent.

Date: Oct 2, 2007 By: _____

Dr. Frank E. Blondino

EXHIBIT A

Clinical Studies

For all oral spray doses administered, drug was successfully delivered. For the doses in 0.75 mg – 1.0 mg range all subjects obtained alprazolam Cmax concentrations exceeding therapeutic level (5 ng/mL).

AUCs and Cmax reported for the oral spray doses in 0.75 – 1.0 mg range are at least consistent with published results for various formulations of alprazolam tablets.

Clear linear dose-response relationship (as evidenced by the AUC to the last measurable observation; Table 1) was established over the entire range of oral spray doses studied (0.25 mg – 1.0 mg). Importantly, AUC_{last} for the 0.5 mg oral tablet is extremely close to the interpolated value for the 0.5 mg oral spray dose. This finding adds validity to the dose-adjustment of certain pharmacokinetic parameters and statistical comparisons between tablet and oral spray treatment groups.

At 6 minutes (Table 2.1), no subjects had detectable drug levels in the oral tablet groups. In all oral spray groups, drug levels were detected for some subjects.

Time to detectable drug level in the oral spray groups (0.75 mg -1.0 mg range) was 4-6 minutes shorter when compared to the oral tablet (mean of 13.3 minutes). Between-treatment differences were statistically significant.

The highest oral spray dose (1 mg dose administered over the tongue) demonstrated faster absorption when compared to the oral tablet. After dose-adjustment, concentration level

(Table 2.2) and total amount of drug delivered (AUC; Table 4.2) by 15 minutes post-dosing were approximately 40 % higher than in the oral tablet group. Without dose-adjustment, percent of Cmax achieved during earlier time points (Table 3) was higher for the 1 mg oral spray (over the tongue) group when compared to the oral tablet (at 12 minutes - 38.5% and 18.8%, respectively with a statistically significant difference).

Analysis of pharmacodynamic data indicates a dose-response relationship for the Anxiety/Tension (Table 5.1) and Sleepiness/Drowsiness (Table 5.2) levels at 30 and 60 minutes post-dosing. Oral spray groups consistently outperformed oral tablet with statistically significant differences reported for the number of pharmacodynamic parameters.

STUDY RESULTS

TABLE 1 Pharmacokinetic Parameters

	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (O/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
Cmax (ng/mL) Mean (SE) Median	3.81 (0.28) 3.37	9.46 (0.62) 9.31	15.90 (1.50) 15.20	13.28 (1.43) 12.40	8.74 (0.54) 8.89
Tmax (h) Mean (SE) Median	91.7 (17.2) 120.0	106.7 (22.8) 90.0	76.7 (25.9) 30.0	125.6 (29.5) 120.0	50.0 (9.2) 45.0
AUC_{last} [(ng/mL)*h] Mean (SE) Median	55.9 (5.8) 50.6	151.2 (12.5) 148.2	209.4 (23.5) 187.4	208.5 (23.6) 200.1	104.0 (7.9) 101.0
Time to Level >= 0 ng/mL (Min) Mean	14.6	8.7* (p=0.04)	7.7*(p=0.01)	7.3*(p=0.01)	13.3
Time to Level >= 5 ng/mL (Min) Mean	45.0	47.8	15.0*(p=0.03)	24.9	34.7
Time to Level >= 5 ng/mL (Min) (ADJUSTED to 1.0 mg DOSE) Mean	31.8	41.1	15.0	24.9	23.8

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
* Statistically significantly different from tablet

TABLE 2.1 Concentration Levels by Treatment Group (Early Time points)

Concentration (ng/mL)	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (O/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
3 min					
Mean (SE)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.09 (0.09)	0.0 (0.0)
Median	0.0	0.0	0.0	0.0	0.0
6 min					
Mean (SE)	0.06 (0.06)	0.23 (0.12)	0.66 (0.24)	0.36 (0.15)	0.0 (0.0)
Median	0.0	0.0	0.51	0.0	0.0
9 min					
Mean (SE)	0.31 (0.18)	0.71 (0.15)	2.72 (1.01)	1.46 (0.32)	0.59 (0.28)
Median	0.0	0.92	2.00	0.97	0.0
12 min					
Mean (SE)	0.73 (0.37)	1.31 (0.13)	6.98 (2.45)	3.66 (0.85)	1.77 (0.64)
Median	0.0	1.31	4.20	3.09	1.48
15 min					
Mean (SE)	1.29 (0.45)	2.10 (0.23)	9.72 (2.56)	5.68 (1.47)	3.36 (1.17)
Median	0.82	1.88	5.99	3.93	2.11
20 min					
Mean (SE)	1.75 (0.42)	3.57 (0.72)	12.68 (2.17)	8.14 (2.16)	4.74 (1.40)
Median	1.27	2.73	13.30	5.05	3.26
30 min					
Mean (SE)	2.27 (0.35)	5.10 (1.04)	13.58 (1.80)	9.51 (1.32)	6.45 (0.96)
Median	2.41	4.32	12.70	10.59	7.60
45 min					
Mean (SE)	2.81 (0.44)	6.62 (0.98)	12.70 (1.44)	9.69 (1.09)	7.08 (0.61)
Median	2.61	8.25	11.80	9.90	7.68

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue

TABLE 2.2 Dose-Adjusted Concentration Levels by Treatment Group (Early Time points)

Dose-Adjusted Concentration (ng/mL)	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (O/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
3 min					
Mean (SE)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.09 (0.09)	0.0 (0.0)
Median	0.0	0.0	0.0	0.0	0.0
6 min					
Mean (SE)	0.22 (0.22)	0.30 (0.16)	0.66* (0.24)	0.36 (0.15)	0.0 (0.0)
Median	0.0	0.0	0.51	0.0	0.0
9 min			(p=0.092)		
Mean (SE)	1.23 (0.70)	0.95 (0.19)	2.72 (1.01)	1.46 (0.32)	1.19 (0.57)
Median	0.0	1.22	2.00	0.97	0.0
12 min			(p=0.103)		
Mean (SE)	2.94 (1.49)	1.74 (0.18)	6.98 (2.45)	3.66 (0.85)	3.55 (1.27)
Median	0.0	1.74	4.20	3.09	2.96
15 min					
Mean (SE)	5.15 (1.78)	2.80 (0.31)	9.72 (2.56)	5.68 (1.47)	6.71 (2.34)
Median	3.28	2.50	5.99	3.93	4.22
20 min					
Mean (SE)	6.98 (1.68)	4.75 (0.95)	12.68 (2.17)	8.14 (2.16)	9.49 (2.80)
Median	5.08	3.63	13.30	5.05	6.52
30 min					
Mean (SE)	9.08 (1.40)	6.79 (1.38)	13.58 (1.80)	9.51** (1.32)	12.90 (1.93)
Median	9.64	5.75	12.70	10.59	15.20
45 min					
Mean (SE)	11.23 (1.78)	8.81** (1.30)	12.70 (1.44)	9.69** (1.09)	14.16 (1.22)
Median	10.44	10.97	11.80	9.90	15.36

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
* Statistically significantly different from tablet
** Statistically significantly different from tablet, but tablet is better (higher concentration)

TABLE 3. Percent of Cmax by Treatment Group (Early Time points)

Percent of Cmax (%)	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (O/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
6 min					
Mean (SE)	1.3 (1.3)	2.1 (1.1)	3.9* (1.3)	2.4 (1.0)	0.0 (0.0)
Median	0.0	0.0	2.8	0.0	0.0
9 min			(p=0.059)		
Mean (SE)	8.0 (4.3)	8.3 (2.2)	15.1 (3.8)	10.6 (1.9)	6.4 (2.9)
Median	0.0	8.1	16.8	9.4	0.0
12 min					
Mean (SE)	18.6 (8.9)	14.7 (2.5)	38.5* (9.5)	25.7 (4.0)	18.8 (6.3)
Median	0.0	12.4	25.5	19.3	17.1
15 min					
Mean (SE)	33.9 (11.3)	23.8 (4.3)	56.2 (10.3)	39.4 (6.8)	35.2 (11.3)
Median	18.1	20.3	37.3	31.2	25.1
20 min			(p=0.074)		
Mean (SE)	46.6 (10.7)	38.5 (7.1)	77.0 (8.1)	56.6 (10.3)	50.6 (13.5)
Median	32.6	30.0	87.5	47.7	37.6
30 min					
Mean (SE)	60.7 (9.4)	54.7 (10.1)	84.2 (4.6)	70.9 (7.2)	71.3 (9.3)
Median	60.5	48.9	83.2	72.8	81.2

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
* Statistically significantly different from tablet

TABLE 4.1 Areas-under-the-Curve (AUC) by Treatment Group (Early Time points)

AUC [(ng/mL)*hr]	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (O/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
9 min					
Mean (SE)	0.02 (0.01)	0.05 (0.01)	0.14 (0.04)	0.10 (0.02)	0.04(0.02)
Median	0.0	0.07	0.12	0.07	0.0
12 min					
Mean (SE)	0.05 (0.02)	0.12 (0.01)	0.40 (0.12)	0.23 (0.04)	0.14 (0.04)
Median	0.0	0.13	0.33	0.17	0.12
15 min					
Mean (SE)	0.13 (0.04)	0.21 (0.02)	0.82 (0.24)	0.46 (0.09)	0.28 (0.08)
Median	0.10	0.20	0.61	0.40	0.21
20 min					
Mean (SE)	0.26 (0.07)	0.43 (0.05)	1.71 (0.42)	1.01 (0.23)	0.61 (0.18)
Median	0.19	0.38	1.13	0.86	0.45
30 min					
Mean (SE)	0.61 (0.13)	1.17 (0.19)	3.94 (0.73)	2.51 (0.50)	1.57 (0.35)
Median	0.50	1.09	3.53	2.24	1.12

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue

TABLE 4.2 Dose-Adjusted Areas-under-the-Curve (AUC) by Treatment Group (Early Time points)

AUC [(ng/mL)*hr]	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (O/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
9 min					
Mean (SE)	0.08 (0.04)	0.07 (0.02)	0.14 (0.04)	0.10 (0.02)	0.09(0.04)
Median	0.0	0.09	0.12	0.07	0.0
12 min					
Mean (SE)	0.20 (0.09)	0.16 (0.01)	0.40 (0.12)	0.23 (0.04)	0.27 (0.08)
Median	0.0	0.17	0.33	0.17	0.24
15 min					
Mean (SE)	0.50 (0.16)	0.27 (0.02)	0.82 (0.24)	0.46 (0.09)	0.57 (0.16)
Median	0.41	0.27	0.61	0.40	0.42
20 min					
Mean (SE)	1.04 (0.28)	0.58 (0.06)	1.71 (0.42)	1.01 (0.23)	1.21 (0.36)
Median	0.74	0.50	1.13	0.86	0.90
30 min					
Mean (SE)	2.45 (0.50)	1.56 (0.25)	3.94 (0.73)	2.51 (0.50)	3.14 (0.70)
Median	2.00	1.44	3.53	2.24	2.25

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue

TABLE 5.1 Anxiety/Tension Level by Time points

Anxiety/Tension Score	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (0/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
30 min			(p=0.074)		
Mean (SE)	3.78 (0.28)	4.0 (0.24)	4.33 (0.33)	4.44* (0.24)	3.67 (0.17)
Median	4.0	4.0	5.0	5.0	4.0
60 min					
Mean (SE)	4.44 (0.18)	4.67 (0.17)	4.33 (0.37)	5.0* (0.0)	4.33 (0.24)
Median	4.0	5.0	5.0	5.0	4.0

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
Anxiety/Tension level is derived from the 5-point self-assessment scale (from 1= "Much More Tense/Anxious" to 5="Much More Relaxed")
* Statistically significantly different from tablet

TABLE 5.2 Sleepiness/Drowsiness Level by Time points

Sleepiness /Drowsiness Score	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (0/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
30 min					
Mean (SE)	2.22 (0.15)	2.44 (0.18)	1.78* (0.36)	1.67* (0.17)	2.67 (0.17)
Median	2.0	2.0	1.0	2.0	3.0
60 min					
Mean (SE)	1.89 (0.11)	1.56* (0.24)	1.11* (0.11)	1.00* (0.0)	2.11 (0.11)
Median	2.0	1.0	1.0	1.0	2.0

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
Sleepiness/Drowsiness level is derived from the 5-point self-assessment scale (from 1= "Much More Sleepy/Drowsy" to 5="Much More Alert")
* Statistically significantly different from tablet

TABLE 6.1 Percent of "Much More Relaxed" Subjects by Time points

Percent of "Much More Relaxed" Subjects	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (0/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
30 min Percent	11.1	22.2	55.6*	55.6*	0.0
60 min Percent	44.4	66.7	66.7	100.0*	44.4

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
Anxiety/Tension level is derived from the 5-point self-assessment scale (from 1= "Much More Tense/Anxious" to 5="Much More Relaxed")
* Statistically significantly different from tablet

TABLE 6.2 Percent of "Much More Sleepy/Drowsy" Subjects by Time points

Percent of "Much More Sleepy/Drowsy" Subjects	0.25 mg Spray (N=9)	0.75 mg Spray (N=9)	1.0 mg Spray (0/T) (N=9)	1.0 mg Spray (U/T) (N=9)	0.5 mg Tablet (N=9)
30 min Percent	0.0	0.0	55.6*	33.3	0.0
60 min Percent	11.1	55.6*	88.9*	100.0*	0.0

NOTES:
O/T = Over-the-Tongue
U/T = Under-the-Tongue
Sleepiness/Drowsiness level is derived from the 5-point self-assessment scale (from 1= "Much More Sleepy/Drowsy" to 5="Much More Alert")
* Statistically significantly different from tablet